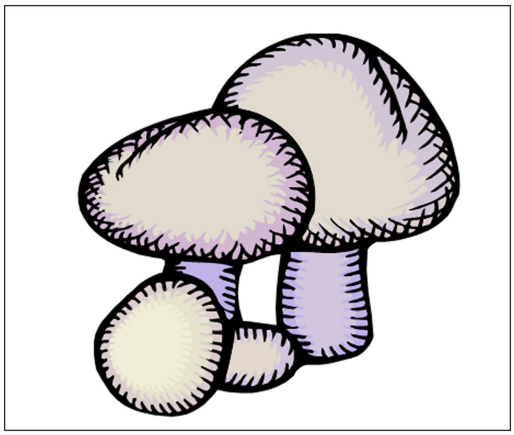
Cell PRESS
Chemistry & Biology

In This Issue



Origins of Secondary Metabolites: A Fungal Perspective

PAGE 792

Endophytes are microorganisms that are ubiquitous in plants and have the capability to biosynthesize a plethora of natural products. Here, Kusari et al. highlight the basic principles of chemical communication strategies of endophytic fungi and emphasize virtually inexhaustible possibilities for secondary metabolite discovery.

RNR Forced into Hexamers

PAGE 799

Ribonucleotide reductase (RNR) is on one of life's most essential enzymes. Work by Aye et al. examines in vivo biochemical mechanism of the leukemia drug Clofarabine and shows that the drug taps into a previously unreported RNR regulatory pathway by causing a persistent alteration of RNR quaternary structure.

Modulating HNF4α

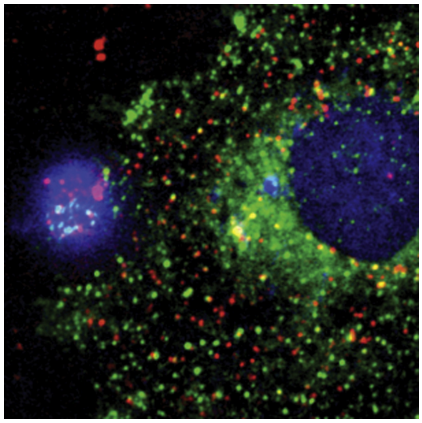
PAGE 806

HNF4α is nuclear receptor transcription factor that plays a central role in differentiation and cellular metabolism. Natural ligands for HNF4α are fatty acids, but there is little evidence that they regulate HNF4α. Now, Kiselyuk et al. describe small-molecule HNF4α antagonists and characterize their activity.

Helping Miniatures Escape

PAGE 819

Appelbaum et al. explore the structural determinants and stepwise pathway by which certain cationic proteins and peptides cross membranes to access the cytoplasm, providing the groundwork for engineering cytosol-directing arginine arrangements into proteins, peptides, and peptidomimetics.



Delivering the Supercharged

PAGE 831

Supercharged proteins can deliver functional macromolecules into the cytoplasm of mammalian cells with potencies that exceed those of cationic peptides. Thompson et al. generated a series of supercharged GFPs with varying net charge and evaluated their cellular uptake and protein delivery capabilities.

Sensitizing *Mycobacterium tuberculosis*

PAGE 844

Abrahams et al. use target-based whole-cell screening to identify compounds with known mechanisms of action by generating mutants of *M. tuberculosis* that conditionally express different targets and identify compounds with greater potency against a strain with pantothenate synthetase deletion as a validation.

Mobile Flavin Gets Caught

PAGE 855

Some natural product diversity arises from tailoring of common molecular scaffolds. Enzymatic pathways for these scaffolds are often duplicated and modified to generate diversity. Now, Goldman et al. describe a mechanism of using the same platform to produce two different molecular scaffolds, rebeccamycin and staurosporine.

In This Issue

In Vivo FRET-Biosensors for Prenylation

PAGE 866

Köhnke et al. present a high-throughput amenable cell-based FRET assay for identifying inhibitors of functionally essential Ras nanoclusters found in the membrane and demonstrate that Rab proteins are also nanoclustered, underscoring the significance of the approach to target other small GTPases.

Exosite Targeting on Anthrax Lethal Factor

PAGE 875

Conventional protease inhibitor discovery is strongly biased towards compounds that bind at the active site. Bannwarth et al. apply an alternative strategy and use HTS to discover exosite-targeting inhibitors of the metalloproteinase anthrax lethal factor, thus validating the approach based on targeting regions outside of the active site.

Antibiotic Poisoning the Host

PAGE 883

5-nitrofurans are antibiotics activated by pathogen-specific enzymes; however, less is known about what happens in the host. Zhou et al. identify aldehyde dehydrogenase (ALDH) 2 as a 5-nitrofuran-activating enzyme that has implications for managing some of the toxicity associated with 5-nitrofuran treatment.

Fission Yeast for Chemical Biology

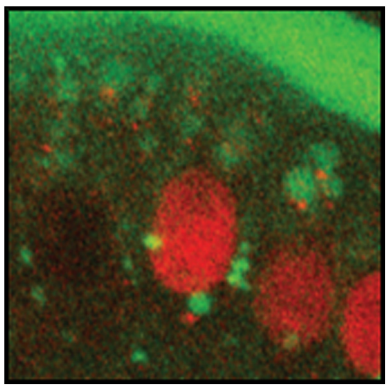
PAGE 893

Fission yeast use for chemical biology has been limited by its robust multidrug resistance (MDR) response. Kawashima et al. identify key cellular factors responsible for MDR and design strains sensitive to a wide-range of chemical inhibitors, thus enabling chemical biology work in this model system.

Beyond the Optical Diffraction Limit

PAGE 902

Ondrus et al. develop and apply selective fluorescent agents that bind to sodium channels and use state-of-the-art cell imaging to view movement and distribution of sodium channels within the outer membrane of cells at an unparalleled level of visual resolution, seeing how nerve cells conduct electricity.



Resource: Visualizing Lipid Metabolism

PAGE 913

Walters et al. develop a method to study intestinal enterocyte lipid uptake at single-cell resolution in a living vertebrate, the larval zebrafish. They suggest that the mechanism for coupled cholesterol and fatty acid uptake occurs through the dynamic localization of NPC1L1.

